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EXAMINER
RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/983,025	OXVIG ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,17-19,30-47,49-52,55-58,62,70,75,83,85,87 and 90-100* is/are pending in the application.

4a) Of the above claim(s) *30-47,49-52,55-58,62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12,17-19,75,83,90-93 and 95-100* is/are rejected.

7)☒ Claim(s) *70,85,87 and 94* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/22/201* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 12, 17-19, 30-47, 49-52, 55-58, 62, 70, 75, 83, 85, 87, 90-100 are pending.

Applicant's amendment of claims 12, 17-19, 62, 75, 83, 85, 87, cancellation of claims 53, 59, 71-74, 76-82, 84, 86, 88-89, and addition of claims 90-100 in a communication filed on 6/10/2004 are acknowledged.

The pending product claims are not in condition for allowance at this time. This application contains claims 30-47, 49-52, 55-58, 62 drawn to an invention non-elected with traverse in a communication filed on 11/24/2003. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

New claims 90-100 are directed to the elected invention, i.e. the polypeptide of SEQ ID NO: 2, and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claims 17, 90, 92, 93, 95, 100 are objected to due to the recitation of "PAPP-A2". As indicated previously, abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the term "pregnancy associated plasma protein A2" be recited at least once. Appropriate correction is required.

2. Claim 70 is objected to due to the recitation of "polypeptide according to (a), 9b), …". It appears that this is a typographical error. Appropriate correction is required.

3. Claim 91 is objected to due to the recitation of "fragment according to (1). For clarity, it is suggested that the term be amended to recite "(1)(b)". Appropriate correction is required.

4. Claim 96 is objected to due to the recitation of "AA". As indicated previously, abbreviations unless otherwise obvious and/or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. It is suggested that the term "AA" be replaced with "amino acids". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 17, 93, 95, 100 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 17 is indefinite in the recitation of "the polypeptide of claim 12 wherein the prepro part of PAPP-A2 is operably linked to the mature part of PAPP-A2 corresponding to amino acid residues 234 to 1791 of SEQ ID NO: 1" for the following reasons. While the term "mature part of PAPP-A2 corresponding to amino acids…" is clear as the claims further defines it by specific amino acid residues within SEQ ID NO: 2, the term "prepro part of PAPP-A2" is unclear as one cannot determine if the intended prepro part is that of any PAPP-A2 (i.e. from any source) or if it refers to residues 1-233 of the polypeptide of SEQ ID NO: 2, as is the case with the mature part of PAPP-A2. For examination purposes, it will be assumed that the term "prepro part of PAPP-A2" refers to residues 1-233 of the polypeptide of SEQ ID NO: 2. Correction is required.

8. Claim 93 is indefinite in the recitation of "comprises at least 75% of mature PAPP-A2" as it is unclear if the term refers to structure or activity. If it refers to structure, 75% of amino acids 234-1791 is equivalent to 1169 amino acids (0.75x 1558). For examination purposes, it will be interpreted as "comprises at least 1169 consecutive amino acids of the fragment consisting of residues 234-1791 of the

polypeptide of SEQ ID NO: 1". In the instant case, claim 93 cannot be interpreted as directed to a fragment which is at least 75% sequence identical to amino acids 234-1791 of the polypeptide of SEQ ID NO: 2" due to the fact that claim 90 (1)(b), from which claim 93 ultimately depend, is directed to a fragment of amino acid residues 234-1791 of SEQ ID NO: 2. Therefore, since it is a fragment of residues 234-1791 of SEQ ID NO: 2, only 100% sequence identity is possible. Correction is required.

9. Claim 95 is indefinite in the recitation of "which comprises....consensus sequence LNR 1-3, SCR 1-5, and all cysteine...." as it is unclear which consensus sequences are being referred to absent a sequence identifier which corresponds to those consensus sequences. It is suggested that if the sequence listing provides a sequence identifier for each of the consensus sequences recited, those sequence identifiers be included in the claim. In the alternative, Applicants may refer to specific residues in SEQ ID NO: 2 which correspond to the consensus sequences recited as long as there is adequate support in the specification. For examination purposes, no patentable weight will be given to the term "consensus sequence LNR 1-3, SCR 1-5" and the claim will be interpreted to recite "which comprises all cysteine residues....". Correction is required.

10. Claim 100 is indefinite in the recitation of "the polypeptide of ...which is a processing variant of mature PAPP-A2" for the following reasons. As written, it is unclear as to whether a processing variant only includes fragments of amino acids 234-1791 of the polypeptide of SEQ ID NO: 2. It is noted that while the specification provides a definition for processing variants as variants resulting from alternative processing events, it does not limit the processing events to proteolysis. As such, it can include the linkage of other polypeptides to mature PAPP-A2. For examination purposes, it will be assumed that the term reads "which is a fragment of amino acids 234-1791 of the polypeptide of SEQ ID NO: 2 that results from intracellular proteolysis". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. New claims 90-91, 93, 95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 90-91 are directed in part to a fragment of at least 6 amino acids of the residues 234-1791 of SEQ ID NO: 2. Claim 90 is also directed to a fusion protein comprising amino acids 234-1791 of SEQ ID NO: 2, wherein said fusion is not a pregnancy associated plasma protein. Claim 93 is directed to a fragment of at least 1196 consecutive amino acids of residues 234-1791 of SEQ ID NO: 2 (see Claim Rejections under 35 USC 112, second paragraph for claim interpretation). Claim 95 is directed to a consensus sequence LNR 3. The Examiner is unable to locate adequate support in the specification for (1) a fragment of at least 6 amino acids of residues 234-1791 of SEQ ID NO: 2, (2) a fusion protein comprising amino acids 234-1791 of SEQ ID NO: 2 wherein said fusion is not a pregnancy associated plasma protein, (3) a fragment of at least 1196 consecutive amino acids of residues 234-1791 of SEQ ID NO: 2, or (4) a consensus sequence labeled LNR 3. The Examiner has considered Applicant's remarks regarding support for these new claims, however the pages provided in support of these new claims do not seem to provide such support. See, for example, Figure 3, where there is no disclosure of LNR 3. Also, it is noted that while there is support in the specification for a fragment of at least 7 amino acids of residues 234-1791 of SEQ ID NO: 2, there is no support for a fragment of at least 6 amino acids as recited in claim 90. Furthermore, while there is support for a fusion protein comprising residues 234-1791 of SEQ

ID NO: 2 and either a GST tag, c-myc epitope, histidine tag, or keyhole limpet hemocyanin, there is no support for fusion proteins which exclude pregnancy associated plasma proteins. In regard to claim 93, while the instant rejection is based on the claim's interpretation, it is noted that while there is support for "75% sequence identity", this limitation cannot be read in the claim as currently written for the reasons indicated above. Thus, there is no indication that the subject matter of claims 90-91, 93 and 95 were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

13. Claims 12, 18-19, 75, 83 remain rejected and new claims 97-99 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in a Non Final Action mailed on 2/10/2004.

14. Applicants argue that the claims as amended are more stringent since they recite at least 97% sequence identity. Furthermore, Applicants argue that the specification discloses several fragments of the polypeptide of SEQ ID NO: 2.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 12, 18-19, 75, 83 or avoid the rejection of new claims 97-99. Claims 12, 18-19, 75, 83 are directed in part to a genus of polypeptides of any function (a) having at least 97% sequence identity to SEQ ID NO: 2 or amino acids 234-1791 of SEQ ID NO: 2, or (b) comprising residues 234-1791 of SEQ ID NO: 2 with any number of conservative substitutions, wherein said polypeptides are recognized by an antibody which recognizes the polypeptide of SEQ ID NO: 2 or bind to a cell surface receptor with affinity for the polypeptide of SEQ ID NO: 2. It is noted that the functional limitation recited in claim 12

i), i.e. proteolytic activity specific for at least IGFBP-5, is an alternative limitation due to the recitation of "and/or". Claims 97-99 are directed to a genus of polypeptides of any function comprising amino acids 1-22, 23-233, or 1-233 of SEQ ID NO: 2. While the specification discloses that the polypeptide of SEQ ID NO: 2 cleaves IGFBP-5 (insulin like growth factor binding protein 5), the specification is silent in regard to other functions associated with structural homologs of the polypeptide of SEQ ID NO: 2, such as those recited in the claims. In addition, the specification is silent in regard to which specific amino acids in the polypeptide of SEQ ID NO: 2 can be conservatively substituted and still retain the only biological function disclosed, i.e. cleavage of IGFBP-5. In regard to claims 97-99, while the specification discloses the specific amino acid residues of SEQ ID NO: 2 recited as corresponding to the signal peptide, and the prepro part of the PAPP-A2 disclosed, it is noted that these fragments do not have the activity of the mature PAPP-A2 polypeptide, i.e. cleavage of IGFBP-5. The genus of polypeptides of claims 97-99 do not have structural features which constitute a substantial portion of the genus since the remainder of any polypeptide comprising said structural features is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Furthermore, the genus of polypeptides claimed have the potentiality of encoding polypeptides of different functions, even if the structural similarity among the species encompassed by the genus is high. As indicated in the previous Office Action, the art teaches examples of how even small amino acid changes in a protein can drastically change function. See particularly, the teachings of Witkowski et al., Broun et al., and Seffernick et al. already discussed. Thus, one cannot reasonably conclude that the disclosure of a single species, i.e. the polypeptide of SEQ ID NO: 2, is sufficient to adequately describe the claimed genus of polypeptides.

16. Claim 12, 18-19, 75, 83 remain rejected and new claims 97-99 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (1) a polypeptide comprising SEQ ID

NO: 2, and (2) fragments of the polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for (a) a polypeptide of any function having at least 97% sequence identity to the polypeptide of SEQ ID NO: 2 or residues 234-1791 of SEQ ID NO: 2, (b) a polypeptide of any function having the amino acid sequence of SEQ ID NO: 2, wherein said polypeptide have any number of conservative substitutions, or (c) a polypeptide of any function comprising amino acids 1-22, 23-233, or 1-233 of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in a Non Final Action mailed on 2/10/2004.

17. Applicants argue that claim 12 now requires that the mutants be at least 97% identical to the recited protein. Thus, it is Applicant's contention that given the high % identity claimed, the Examiner should not have a reasonable basis to doubt enablement. Applicants also refer to page 52 of the specification to indicate that motifs of PAPP-A associated with activity have been identified.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 12, 18-19, 75, 83 or avoid the rejection of new claims 97-99. The Examiner acknowledges the teachings of the specification, and the amendments to the claims which now recite a high % sequence identity. However, as indicated previously, the genus of polypeptides claimed encompasses polypeptides of any function, in view of the recitation of "and/or". The functional limitation recited is in the alternative form. Therefore, the claims encompass polypeptides which would need to meet the structural limitations recited but do not necessarily require the function disclosed, i.e. cleavage of IGFBP-5. No other functions have been disclosed for the genus of polypeptides claimed. In addition, it is reiterated herein that the specification fails to teach which amino acids in the polypeptide of SEQ ID NO: 2 can be conservatively substituted, which amino acids to substitute with, and still retain the ability to cleave IGFBP-5. It is noted that the specification teaches that while PAPP-A proteins have proteolytic activity, the substrate can be different, as is the case with PAPP-A and PAPP-A2 (e.g. IGFBP-4 vs

IGFBP-5). As previously discussed even small structural changes can lead to significant changes in function. See, for example, the teachings of Witkowski et al. where it is shown that a single conservative amino acid substitution, cysteine to glutamine, leads to a protein of different function. Therefore, in the absence of any teaching correlating structure with function, it is unclear as to how one of skill in the art can determine from the structure disclosed, which of the structural homologs recited are going to have the same proteolytic function as that of the polypeptide of SEQ ID NO: 2.

In regard to claims encompassing polypeptides comprising the signal peptide or the prepro part of the polypeptide of SEQ ID NO: 2, it is noted that the specification fails to disclose other functions for those polypeptides. It is also noted that the specification does not disclose cleavage of IGFBP-5 with the signal peptide or the prepro part of the polypeptide of SEQ ID NO: 2. As indicated above, the genus of polypeptides comprising these specific fragments of the polypeptide of SEQ ID NO: 2 can encompass polypeptides of any function. In the absence of a specific function for these polypeptides, it is unclear as to how one of skill in the art can use these polypeptides. In view of what is disclosed by the specification, and the teachings of the art in regard to assigning function based solely in structural homology, determining the function of these polypeptides would impose the burden of undue experimentation. Therefore, one of skill in the art cannot reasonably conclude that the specification is enabling for the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

19. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

20. Claims 12, 18-19, 75 remain rejected and new claims 90, 91, 92, 96 are rejected under 35 U.S.C. 102(a) as being anticipated by Farr et al. (Biochim. Biophys. Acta, 1493:356-362, October 2, 2000; cited in the IDS; SPTREMBL accession number Q9H4C9).

21. Applicants argue that the claims as amended are not anticipated by the teachings of Farr et al. Applicants submit that the polypeptide of Farr et al. is 95.63% sequence identical to the polypeptide of claim 12 (b), which is less than 97%.

22. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 12, 18-19 or avoid the rejection of new claims 90-92, 96. Claims 12, 18-19 and 75 are now directed in part to an isolated polypeptide which is at least 97% sequence identical to a polypeptide which consists of residues 234-1791 of SEQ ID NO: 2 As indicated previously, Farr et al. teaches a polypeptide called PAPP-E which is 1624 amino acids long and comprises amino acids 168-1791 of SEQ ID NO: 2 except for 4 mismatches corresponding to positions 447, 846, 1343, 1739 of SEQ ID NO: 2. Only one of the mismatches is a conservative substitution. See alignment provided in previous Office Action. The polypeptide of Farr et al. is 1624 amino acids long and 99.7% sequence identical to a polypeptide consisting of residues 234-1791 (1558 residues) of SEQ ID NO: 2 (99.7% = 1554 matches x 100 / 1558 residues). Also, since the structural similarity between the polypeptide of Farr et al. and the fragment consisting of residues 234-1791 is extremely high, both polypeptides share a large number of epitopes, thus antibodies raised with epitopes corresponding to residues 67-1624 of the polypeptide of Farr et al. are expected to bind to a polypeptide consisting of residues 234-1791 of SEQ ID NO: 2. Therefore, the polypeptide of Farr et al. anticipate claims 12, 18-19 as written.

Claim 90-92 and 96 are directed in part to fragments of at least 6, 17 or 50 amino acids in length of the polypeptide of SEQ ID NO: 2. Farr et al. also teaches several specific fragments of the polypeptide of SEQ ID NO: 2. Figure 3 (page 360) shows 5 fragments corresponding to short consensus sequences (SCRs), 2 fragments corresponding to Lin-notch repeats (LNR-1 and LNR-2) and 1 fragment which corresponds to a zinc-binding motif. These fragments are identical to fragments of the polypeptide of SEQ ID NO: 2 as follows: SCR-1 (PAPP-E) in Figure 3 correspond to residues 1396-1459 of SEQ ID NO: 2, SCR-2 (PAPP-E) in Figure 3 corresponds to residues 1464-1521 of SEQ ID NO: 2, SCR-3

(PAPP-E) in Figure 3 corresponds to residues 1525-1590 of SEQ ID NO: 2, SCR-4 (PAPP-E) in Figure 3 corresponds to residues 1595-1646, SCR-5 (PAPP-E) in Figure 3 corresponds to residues 1653-1729 of SEQ ID NO: 2, LNR-1 (PAPP-E) in Figure 3 corresponds to residues 586-611 of SEQ ID NO: 2, LNR-2 (PAPP-E) in Figure 3 corresponds to residues 612-644 of SEQ ID NO: 2, and the zinc-binding motif of PAPP-E in Figure 3 corresponds to residues 733-743 of SEQ ID NO: 2. The fragments labeled SCR are all over 50 amino acids in length, the fragments labeled LNR are between 26-33 amino acids in length, and the zinc binding motif is 10 amino acids in length. Therefore, the fragments of Farr et al. anticipate claims 90-92 and 96 as written.

23. It is noted that claim 93 has not been rejected in view of its interpretation, i.e. directed to a fragment comprising at least 1169 consecutive amino acids of residues 234-1791 of SEQ ID NO: 2.

Allowable Subject Matter

24. Claims 70, 85, 87, 94 appear to be allowable over the prior art of record but are objected to since they depend upon a rejected base claim.

Conclusion

25. No claim is in condition for allowance.

26. Applicant's amendment of claims necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action

is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

27. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

28. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 24, 2004